

REMARKS**I. OVERVIEW**

Applicants have reviewed and considered the Office Action dated June 14, 2004, and the references cited therewith. Applicants note that claims 9, 17 and 18 have been previously withdrawn from consideration. Claims 1, and 3 have been amended and claims 20-29 are new. The amendments to the claims are fully supported by the specification as originally filed, and no new matter has been added. The present response is an earnest effort to respond to the Office Action of June 14, 2004. Reconsideration and passage to issuance is therefore respectfully requested.

II. ISSUES UNDER 35 U.S.C. § 112

Claim 3 has been rejected under 35 U.S.C. § 112, second paragraph for being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner is unclear as to how the term "connectivity constraints" serves to further limit claim 1. Claims 1 and 3 have been amended. Claim 3 now requires that "the constraints further include a set of connectivity restraints" and claim 1 has been amended to remove the consisting of language. Thus, it is now clear that the "connectivity restraints" of claim 3 are at least a subset of the constraints of claim 1. Therefore, it is respectfully submitted that claim 3 has been clarified and this rejection has been appropriately remedied.

III. ISSUES UNDER 35 U.S.C. § 102

Claims 1, 3-6, 8, 12-16 and 19 have been rejected under 35 U.S.C. § 102(a) as being anticipated by Edwards et al (IDS ref: BMC Bioinformatics (2000) vol. 1:1, pp. 1-10) (hereinafter "Edwards"). This rejection is respectfully traversed.

Claim 1 as amended requires: "A method for modeling cellular metabolism of an organism, comprising: constructing a flux balance analysis model; applying constraints to the flux balance analysis model, the constraints including qualitative kinetic information constraints." Contrary to the Examiner's assertion, Edwards does not disclose applying "qualitative kinetic information constraints" to a flux balance analysis model. Edwards, does, however, make two statements that the Examiner apparently misconstrues. At p. 2, Edwards discloses:

"While the ultimate goal is the development of dynamic models for the complete simulation of cellular metabolism, the success of such approaches has been severely hampered by the lack of kinetic information on the dynamics and regulation of metabolism. However, in the absence of kinetic information it is still possible to assess the theoretical capabilities and operative modes of metabolism using flux balance analysis (FBA)" (citations omitted).

When taken in proper context, this disclosure merely reiterates the well known divide between two categories of models of cellular metabolism. The first category takes into account kinetic and regulatory information and the second category uses flux balance analysis. It is observed that these categories of models are further described in the BACKGROUND OF THE INVENTION section of the present application. This statement found in Edwards merely refers to there being different approaches to metabolic modeling, one approach using kinetic information and a second approach using flux balance analysis. Thus, this disclosure in Edwards does not support the Examiner's position and does not disclose the use of kinetic information

constraints in a Flux Balance Analysis model, let alone the "qualitative kinetic information constraints" required by claim 1.

The second statement made by Edwards regarding kinetic information is found on page 3.

Edwards states that:

"The feasible set can be further reduced by imposing additional constraints (i.e. kinetic or gene regulatory constraints), and in the limiting condition where all constraints are known, the feasible set may reduce to a single point."

To the extent the Examiner is relying upon this statement, the Examiner is once again taking this statement out of its proper context. The type of kinetic or gene regulatory constraints referred to by Edwards are quantitative constraints such as numerical values for kinetic parameters or regulatory loops. Edwards simply does not disclose any use of qualitative constraints as required by claim 1. It is also observed that Edwards would merely apply these quantitative (not qualitative) constraints to a feasible set. The feasible set of Edwards is created by application of a flux balance analysis model, thus Edwards does not disclose applying kinetic or gene regulatory constraints of any kind to a flux balance analysis model itself, but rather only to a feasible set produced by a flux balance analysis model. Therefore, although Edwards uses similar terminology in some respects, Edwards is directed to a significantly different methodology. In particular, Edwards does not recognize, let alone disclose how qualitative constraints can be applied to a flux balance analysis. Therefore, it is respectfully submitted that this rejection to claim 1 must be withdrawn. As claims 3 and 5 depend from claim 1, it is respectfully submitted that these rejections must also be withdrawn.

Claim 6 requires the step of "applying a plurality of logic constraints to the flux balance analysis model." The Examiner purports that this limitation is disclosed by Edwards. The Examiner is simply mistaken. It is observed that the Examiner does not cite to any specific

disclosure within Edwards which discloses applying a plurality of logic constraints to the flux balance analysis model. Edwards discloses applying cellular constraints to a flux balance analysis model to produce a feasible set. Edwards then discloses the possibility of reducing the feasible set by applying kinetic or gene regulatory constraints. Edwards does not disclose that logic constraints of any kind are used, let alone logic constraints being applied to the flux balance analysis mode. For example, see Figure 1 and its description in Edwards where cellular constraints have specific numeric values and are not logic constraints. One of the advantages of using the logic constraints of the present invention is that when, in response to environmental changes, the metabolic network shifts from one steady-state to another, up or down changes in metabolite concentrations are consistent with up or down changes in reaction fluxes. Thus, through incorporating logic constraints into the FBA model, the model is safeguarded against violation of kinetic and regulatory barriers. Because Edwards not disclose the step of "applying a plurality of logic constraints to the flux balance analysis model" required by claim 6, this rejection must be withdrawn. As claims 8 and 12-16 depend from claim 6, this rejections should also be withdrawn.

There is an independent reason for patentability of claim 8. Claim 8 requires that "the logic constraints are defined by a relationship between changes in reaction fluxes and metabolic concentrations." Edwards does not disclose this relationship either as Edwards not disclose the use of logic constraints.

Claim 19 also requires that the constraints applied to the flux balance analysis model "include qualitative kinetic information constraints." As previously explained, Edwards simply does not use qualitative kinetic information constraints. Therefore this rejection to claim 19 must be withdrawn.

IV. ISSUES UNDER 35 U.S.C. § 103

The Examiner rejects claims 1-8, 10-16 and 19 under 35 U.S.C. § 103(a) as being unpatentable over Edwards et al. (IDS ref: BMC Bioinformatics (2000) vol. 1:1, pages 1-10) in view of Schilling et al. (IDS ref: PNAS (4/1998) vol. 95, pp. 4193-4198) (hereinafter "Schilling"). This rejection is respectfully traversed.

The deficiencies of Edwards relative to the present invention have already been discussed in some detail. Schilling does not remedy these deficiencies. In particular, Schilling does not disclose use of qualitative kinetic information constraints or qualitative regulatory information constraints. Nor does the Examiner indicate that Schilling discloses either the use of qualitative kinetic information constraints or qualitative regulatory information constraints. Thus, neither of the Edwards and Schilling references either alone or combined teach or suggest all the elements of the Applicants' claimed invention, in particular the qualitative kinetic information constraints or the qualitative regulatory information constraints. Therefore these rejections must be withdrawn on that basis.

It is further observed that Edwards actually teaches away from the Applicants' claimed invention. In particular, at p. 8, left column, last paragraph, Edwards specifically discloses that:

"It should be mentioned that FBA does not directly consider regulation, or the regulatory constraints on the metabolic network, but rather FBA assumes that the regulation is such that metabolic behavior is optimal."

Thus, when taken as a whole, it is clear that not only does Edwards not recognize the use of regulatory constraints in a flux balance analysis model, Edwards explicitly teaches that one does not incorporate regulatory constraints into a FBA model.

V. NEW CLAIMS AND CLAIM AMENDMENTS

The present response broadens claim 1 with respect to "qualitative kinetic information constraints" as the qualitative kinetic information constraints need not be selected from a particular set. New claim 23 is also similar to original claim 1, but broadens original claim 1 with respect to "qualitative regulatory information constraints" as the qualitative regulatory information constraints need not be selected from a particular set. Similarly, new claim 29 is also similar to original claim 1, but broadens original claim 1 with respect to "differential DNA microarray experimental data constraints." The support for the additional claims is apparent from the original claims. Upon the Examiner's further review, it should be clear to the Examiner that Edwards does not disclose "qualitative regulatory information constraints" and as the Examiner does not even attempt to cite any reference as disclosing the "differential DNA microarray experimental data constraints" applied to a flux balance analysis model, it is respectfully submitted that all new claims are also in proper form for immediate allowance.

Therefore, it is respectfully submitted that all pending claims are in proper form for immediate allowance. Reconsideration and passage to issuance is therefore respectfully requested.

V. CONCLUSION

Please Charge Deposit Account No. 26-0084 a total of \$185.00 for the 2 new independent claims over three (3) and the 9 claims over 20. No other fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,

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